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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,172	09/13/2003	Jason C. H. Shih	5051-653	7508

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,172	SHIH ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/01/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Restriction requirement filed Nov. 30, 2005 is acknowledged. Claims 14-30 have been canceled. Claims 1-13 directed to the elected invention of a method of making keratinase are pending and under examination.

DETAILED ACTION

1. Objections

Lack of compliance of nucleotide sequence disclosure with 37 C.F.R. 1.821-1.825

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth bellow and on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.

There is no:

1) computer readable form of the sequence listing, and

2) paper form of the sequence listing,

The specification is objected to for lack of catalog number and the full address of the DSM firm of Holland, wherefrom the pLAT8 plasmid was purchased.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

Claims

Claim 1 is objected to because the word "media" in line 2 and 7 is a laboratory jargon and should be replaced with "medium".

2. Rejections

2.1. 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing in reciting "*kerA* coding segment". It is unknown whether Applicants refer to the *kerA* gene as a whole or to its part encoding keratinase. The specification teaches the whole gene *kerA* was used by Applicants in the claimed method. For examination purposes it is assumed that Applicants intention is to claim a method of use of an integrant that comprises in its chromosome a DNA segement, i.e., DNA molecule, encoding keratinase, wherein said DNA segment is a *kerA* gene.

In addition, claim 2 is confusing in recitation of the word "substrate" as it is unclear what substrate the Applicants mean. Do Applicants mean the nutrient in the medium or a keratinase substrate or other substrate?

Claim 3 is unclear in recitation of the term "feather meal". The specification does not define the term "feather meal". Furthermore, the term "soy" as used in the claim is unclear, because it refers to the plant as a whole. It is not clarified which component(s) of the plant is used in the medium.

Claim 11 is indefinite as reciting an indefinite phrase "a protease-deficient *Bacillus*". There are several species of *Bacilli* and each one of them comprises many proteases. It is unknown which protease are the Applicants referring to.

2.2. 35 USC section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

Claim 1-13 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a large and variable genus of methods of using of integrants of *Bacillus* species having at least one heterologous *kerA* gene inserted into their chromosome. The claims are directed to the use of a large genus of transformants comprising one or several copies of any heterologous *kerA* gene. Applicants however disclose only *Bacillus subtilis* species having integrated to its chromosome the *kerA* gene of *Bacillus licheniformis;* see page 5 and Table 2, page 6. Disclosing this one recombinant *Bacillus* species transformed with only one identified *kerA* gene does not provide sufficient identifying characteristics of the genus of *Bacillus* species having one or multiple copies of any *kerA* gene integrated into their chromosome. Applicants' attention is turned to the fact that integrants of *B. licheniformis* they describe contain the homologous *kerA* gene in their chromosome. For the presented reasons, one of skills in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filled.

In addition, claim 6 is rejected because the Applicants fail to teach *kerA* gene of *Bacillus subtillis*. This is a complete lack of written description.

Furthermore, claim 11 imposes limitation on the genus of hosts to be used by the method to only those that a protease-deficient *Bacilli.* The term "protease-deficient *Bacillus*" relates to deficiency of any protease in the cell of any species belonging to the genus *Bacillus*. By teaching B. *licheniformis* T399D asporogenic strain that, as indicated on page 4, second paragraph of the specification is deficient in keratinase,

Applicants do not provide identifying characteristics of the whole genus of host *Bacilli* being deficient in a protease. For that reasons, one of skills in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filled.

Scope of enablement

Claim 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of a recombinant *Bacillus subtilis* having at least one heterologous *kerA* gene of *Bacillus licheniformis* inserted into *B. subtilis'* chromosome, does not reasonably provide enablement for

1) any recombinant Bacillus having any heterologous *kerA* gene inserted into its chromosome, and

2) wherein the host cell is a *Bacillus* deficient for any protease.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breadth of the claims covers use of integrant *Bacillus* wherein

1) said integrant comprises any heterologous *kerA*, wherein the gene is form any natural or man-made source, and

2) the host cell taken for transformation is *Bacillus* deficient for any protease.

Although the knowledge of producing of integrants of bacterial cell, and producing bacterial cells deficient for activity of any protease are well developed, and skills of artisans relatively high, to make the claimed invention involves experimentation which is not routine. It is so because of lack of instruction as to the source of *kerA* gene, and/or its structure, and lack of teaching which protease in *Bacillus* cells used for transformation is to be deficient.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed as to make and use the claimed invention. Specifically, the specification does not instruct as to the structure of any (i.e., all) *kerA* genes to be used. Providing one *kerA* gene of *B. licheniformis* does not provide a guidance as to the structure of all *kerA* gene that are to be used to make the invention. Also, lack of guidance as to which protease should be deficient in the host cell used for integration also imposes on one skilled in the art the experimentation with a low probability of success absent teaching the exact name of the protease, and/or its structure.

In summary, without a guidance regarding the structure/origin of *kerA* gene, and the name/structure of *Bacillus* protease to be deficient in the host cells the experimentation left to skilled artisan is improperly extensive and undue.

2.2. 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1, 4, 6, 7, 9 and 10 are rejected under 35 U.S.C. 103(a) as obvious over Lin et al., (Nucleotide Sequence and Expression of *kerA*, the Gene Encoding a Keratinolytic Protease of *Bacillus licheniforms* PWD-1, Applied and Environmental Microbiology, 1995, 61, 1469-1474, included in the IDS) in view of van der Laan et al. (Cloning, Characterization, and Multiple Chromosomal Integration of a *Bacillus* Alkaline Protease Gene, Applied and Environmental Microbiology, 1991, 57, 901-909, included

in the IDS) and the product of the Dutch Firm DSM, which is integrative plasmid pLAT8 specific for *Bacillus*.

Lin et al. teach the encoding DNA and amino acid sequence of keratinase (serine protease) from *B. licheniformis*. Lin et al., however, do not teach the production of said keratinase in integrants of *Bacillus*.

Van der Laan et al. teach that efficient expression of a serine protease may be achieved in recombinants of *Bacillus subtilis* cells wherein said recombinants have the gene of the protease integrated into their chromosomes. The integrants are more stable than transformants possessing extrachromosomal expression vectors; see the abstract of the article. See also page 905 left column entitled "Production improvement of the alkaline serine protease of strain PB92", where the authors describe production of serine protease of *Bacillus alcalophilus* in *Bacillus subtillis* using integration of the protease gene. Applicants write, page 6, line 4 under Table 2, they used a modified protoplast method of Laan et al. for the integration of *kerA* gene into *Bacillus*.

The Dutch firm DSM produces pLAT8 plasmid, containing alpha–amylase gene of *Bacillus,* which is used for integration of DNA into the chromosome of *Bacillus* by scientific community.

It would have been obvious for one having ordinary skills in the art to have *kerA* gene of Lin et al. and express it by integration to a chromosome of *B. subtillis as* van der Laan et al. did, using a commercially available integration plasmid pLAT8. The motivation would be to obtain a cell stably engineered to produce large quantities of keratinase. The motivation is taught by Lin et al, who point out that keratinase is an

enzyme degrading feather from poultry waste. Thus, the enzyme is of importance for industrial and environmental reasons. The expectation of success is high, because van der Laan proved the successful production of serine protease by integrants of *Bacillus*.

Therefore, the invention claimed in claim 1, 4, 6, 7, 9 and 10 was within the ordinary skill in the art to make and use at the time it was made, and was as a whole, *prima facie* obvious.

In addition, claim 11 is rejected, because although van der Laan does not teach the *Bacillus* used for integration of serine protease is to be a protease deficient, van der Laan et al. do not exclude such host Bacillus cell from their method of integration.

Furthermore, claim 12 and 13 are rejected because it is obvious to use a constitutive promoter for efficient expression of a protein of interest; particularly, the promoter P43 which is known since 1987 and since than has been used for a very efficient expression of heterologous genes in *B. subtilis*, including Shih J et al., WO97/39130 published October 23, 1997, who used it for expression of *kerA* gene of *B. licheniformis* in *B. subtillis*; see page 25.

3. Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP 1600
1600

Application No.: 10/661,172
NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

[x] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

[X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. 1.821(c).

[X] 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

[ ] 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up Raw Sequence Listing.

[ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

[ ] 6. The paper copy of the Sequence Listing is not the same as the computer readable from of the Sequence Listing as required by 37 C.F.R. 1.821(e).

[ ] 7. Other:

Applicant Must Provide:

[x] An initial or substitute computer readable form (CRF) copy of the Sequence Listing.

[ ] An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification.

[X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:
For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For Patent software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE